

REMARKS

This is in response to the Official Action dated January 4, 2010. Applicants submit that this is fully responsive to all outstanding objections and rejections in the instant case; and request further examination, and reconsideration and withdrawal of all outstanding rejections for at least the reasons that follow.

In the present invention, osteoclasts are differentiated in Petri dishes (with M-CSF and RANKL), then detached, numbered and seeded onto osteoblasts. The pending claims have been amended such that claim 1 now specifies that the osteoclasts are seeded as specified in Example 1 of the instant specification at a density of 10 cells/mm².

§ 112 Issue

When read in the context of the specification, Claim 20 is neither vague nor indefinite. Claim 20 recites that the "osteoblasts and/or the osteoclasts are normal, and wherein rheumatoid arthritis has been induced chemically *in situ*...." Throughout the specification, applicants use the term "normal" to refer to healthy animals as a source of osteoblasts and/or osteoclasts for use in the bone models and methods of the instant invention. The osteoblasts and osteoclasts derived from those normal healthy animals are then modified *in situ* or *in vitro* to mimic or assume disease states. Among other things, the bone system model can then be used to study the behavior on bone of various disease states including rheumatoid arthritis, various forms of cancer, osteoporosis, and osteomalacia. (Specification [US 2007/0065803], ¶ 0025).

Specifically with regard to rheumatoid arthritis, the specification states that "the osteoblasts and/or osteoclasts are derived from normal animals, the rheumatoid arthritis then being induced chemically in situ, and/or from knock out animals and/or from transgenic animals for any molecules capable of inducing rheumatoid arthritis..." (Specification [US 2007/0065803], ¶ 0045-0047). While the term "normal animals" might not be explicitly defined within the specification, one skilled in the art would have understood that, as used in the specification, the term "normal animals" refers to those not suffering from the disease under investigation, e.g., rheumatoid arthritis. See also, Specification, ¶ 0041 [osteomalacia]; ¶ 0039 [osteoporosis]. In each case, the specification states that the disease state of interest can be induced by in situ modification of the cells by the addition of various chemical agents. See, e.g., ¶¶ 0042, 0043-0044, and 0047. One skilled in the art would have understood that the use of agents to induce the disease of interest would be necessary only if the animals from which the cells were obtained did not suffer from the specified disease. Accordingly, applicants submit that claim 20 is neither vague nor ambiguous.

Prior Art Issues

The instant claims are novel and non-obvious over the Van Blitterswijk (VB) reference; and are nonobvious over the various combinations of Shibutani, Chambers, Rovira, and the Mulari reference.

VB describes the use of undifferentiated cells, and placing those cells on a matrix. VB fails to disclose a co-culture of osteoblasts and osteoclasts. VB also fails

to disclose the use of osteoblasts at confluence on the support. As there are missing elements, the VB reference fails to anticipate the instant claims.

VB also does not teach the use of a controlled culture having, among other things, the specified concentration of osteoclasts seeded onto osteoblasts. In VB, the undifferentiated cells are those that are not yet differentiated to e.g., osteoblasts and osteoclasts (col. 2, lines 40-45); however, there is nothing in VB reporting or recommending the differentiation of the starting cell population to such cells, let alone in combination and at the specified concentration.

Further, it is well known in the art that osteoclast formation requires the presence of RANK ligand (RANK-L). VB fails to use RANK-L. Thus, one skilled in the art would have understood that the VB method could not have effected *in-vitro* formation of osteoclasts.

One of ordinary skill in the art likewise would not have expected that the VB method would have produced non-resorbing osteoclast-like cells (TRAP positive) in that medium without osteoblasts. Thus, one of ordinary skill in the art would have understood that the culture conditions of the instant claims and those of VB are distinct, and that the methods of VB would not have produced the culture of the instant claims.

None of the cited prior art suggests that a specific density of osteoclast seeded onto osteoblasts and/or osteoblasts nodules could or should be produced, nor that it would have allowed one to obtain a bone system model that mimics the natural bone system, and particularly the human bone system. Neither VB, nor any of the other cited references, alone or in combination, teach or suggest a bone model system with a specific density of osteoclasts deposited onto osteoblasts.

Specifically, none of the cited documents discloses that the density of osteoclast seeded onto osteoblasts is to be equal to 10 cells/mm².

Further, because the VB reference uses undifferentiated cells, one skilled in the art would have immediately appreciated that the method for making load-bearing implants and maxillofacial implants (col. 2, l. 21-27) disclosed therein does not teach or suggest laying down on a matrix osteoblasts *at confluence*, and layering osteoclasts onto the osteoblasts. Rather, VB's use of undifferentiated cells, while at best *potentially* producing osteoblasts and osteoclasts, would be unlikely to produce the structured arrangement of the instant claims, and it certainly would not have been a necessary outcome. Accordingly, VB would not have taught all the elements of the claimed invention, and so it does not anticipate the claimed invention.

Obviousness

Shibutani et al. discloses glass slides coated with an apatite-collagen complex to measure osteoclastic resorption. As acknowledged, the reference does not disclose or suggest that a layer and/or nodule of osteoblasts at confluence could or should be seeded on the glass slide. Further, the reference does not teach or suggest the seeding of osteoclasts on a layer of osteoblasts at confluence.

Applicants acknowledge that the instant rejection is made under §103, and that the principal reference need not teach all elements. However, it is well established that "rejections on obviousness grounds cannot be sustained by mere conclusory statements: instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Ex Parte*

Frye, Appeal No. 2009-006013 (Bd. Pat. App. & Int. Feb. 26, 2010). In this respect, the outstanding obviousness rejections fail.

In order to support a *prima facie* case of obviousness, the rejection must show *why* one skilled in the art would have combined the various elements, in the context in which they found in the prior art, in order to produce the claimed invention. Thus, the supporting references must provide both the elements missing from the claims at issue, and a rational basis for combining them in the same fashion as found in the claims to necessarily arrive at the same claimed invention. Here, no such showing has been made, and the supporting references fail to cure the deficiencies of the principal reference.

Chambers fails to add the missing teaching from Shibutani to arrive at the claimed invention. Chambers is not directed to a bone model system, but rather explores the mechanism by which osteoclasts effect bone resorption. Thus, there is no showing how or why one skilled in the art would have combined the two references; and likewise, there is no showing why, with disparate objectives, one would select the essential elements in combination to arrive at the instant invention. While it has been asserted that the reference makes various statements about the role of osteoblasts, there has been no showing that the reference, taken together with Shibutani would have led one skilled in the art to produce the claimed combination of matrix, osteoblasts at confluence, and osteoclasts; nor is there any showing or suggestion that the osteoclasts should be added at the cell density now specified.

Further, applicants have already shown, and it has not been refuted, that Chambers' speculation as to the role of osteoblasts, to the extent it is relevant, has been disproved.

Rovira et al. likewise fails to cure the deficiencies of Shibutani, alone or in combination with Chambers. Rovira fails to describe a bone system model for diagnosing or assaying therapies for bone related maladies involving: a matrix, osteoblasts (or nodules) at confluence, and osteoclasts layered on top, as claimed here.

Claim 20 has been rejected over Shibutani, Chambers, and Rovira, as combined above, and further in view of Traianedes. It is acknowledged that Shibutani, Chambers, and Rovira fail to disclose or suggest induction of rheumatoid arthritis in the bone system model, but that Traianedes provides that teaching.

Applicants traverse the rejection, and urge, as above, that Shibutani, Chambers and Rovira all fail to teach or suggest the subject matter of claims 1-4. The reliance on Traianedes fails to cure the deficiencies of those references with respect to claim 20.

Traianedes describes an effect of the leukotrienes and other metabolites on osteoblast function. Their data includes osteoblast cell cultures and organ culture. The authors reference rheumatoid arthritis; however, the mere reference to the disease does not support a *prima facie* case of obviousness. The rejection fails to state how the cited study, in combination with the other references, suggests the claimed invention. Traianedes provides no teaching or suggestion for constructing the claimed invention, or using it as disclosed. Without such a showing, the rejection must fail.

Claim 17 has been rejected over Shibutani, Chambers, and Rovira, as combined above, and further in view of Rodan. It is acknowledged that Shibutani, Chambers, and Rovira fail to disclose or suggest the use of the claimed system for testing a substance, but argues that Rodan provides that teaching.

Applicants traverse the rejection, and urge, as above, that Shibutani, Chambers and Rovira all fail to teach or suggest the subject matter of claims 1-4. The combination of those references with Rodan fails to cure the deficiencies of those references with respect to claim 17, and so the rejection fails.

Rodan does not disclose assaying compounds on a population as recited in the instant claims, e.g., mineralized matrix, layers or nodules of osteoblasts, and a layer of osteoclasts.

Claim 6 has been rejected over Shibutani, Chambers, and Rovira, as combined above, and further in view of Choi et al. It is acknowledged that Shibutani, Chambers, and Rovira fail to disclose or suggest the use of genetically modified osteoclasts in the claimed system, but argues that Choi provides that teaching.

Applicants traverse the rejection, and urge, as above, that Shibutani, Chambers and Rovira all fail to teach or suggest the subject matter of claims 1-4. The combination of those references with Choi fails to cure the deficiencies of those references with regard to claim 6.

Choi discloses methods and compositions that modulate the activity of cells such as osteoblast cells (see abstract). Choi discloses a molecule called OSCAR identified in osteoclast cells, and describes means for studying its activity. Choi does not disclose or suggest any system as defined in claim 1. Moreover, the reference

fails to suggest the use of a genetically modified cell in the system of the present invention. Accordingly, the rejection fails to support a *prima facie* of obviousness.

Claim 5 has been rejected over Shibutani, Chambers, and Rovira, as combined above, and further in view of Sun et al. It is acknowledged that Shibutani, Chambers, and Rovira fail to disclose or suggest the use of osteoclasts to osteoblasts in the ratio of 1/10 to 1/25, but argues that Sun provides that teaching.

Applicants traverse the rejection, and urge, as above, that Shibutani, Chambers and Rovira all fail to teach or suggest the subject matter of claims 1-4. The combination of those references with Sun fails to cure the deficiencies of those references with regard to claim 5.

Sun studied the effect of hydroxyapatite size on the ratio of osteoblasts to osteoclasts, but does not teach or suggest the claimed ratio. Accordingly, the combination fails to teach or suggest the claimed invention.

Finally, applicants invite the examiner's attention to the fact that none of the cited references discloses or suggests that osteoclasts, which are ten times the size of osteoblasts, could or would migrate through the joint population of osteoblasts to effect resorption activity directly on the bone matrix. Without such an understanding or expectation, there would have been no reasoned basis for constructing or employing the system as claimed. Therefore the subject-matter of the claim set is not obvious over the cited references.

Conclusion

For at least the foregoing reasons, applicants submit that the pending claims are in condition for allowance. Applicant respectfully requests that the Examiner

reconsider and withdraw the outstanding rejections and objections, and allow the present application.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned attorney. Such informal communication will expedite examination and disposition of the application.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

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